

Oropharyngeal cancer: an emergent disease?

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Abstract

Oropharyngeal cancer incidence has recently increased, thereby attracting public attention. Akin to other malignancies of the upper aerodigestive tract, it has been attributed to the carcinogenic effects of tobacco and alcohol use. However, recent evidence shows that a substantial increase in the disease is attributable to the effects of human papillomavirus (HPV). Marked progress has been made in relation to the knowledge of molecular and genetic mechanisms involved in the genesis and progression of these cancers. This has led to the development of new and promising therapies of a more specific and less toxic nature that have prolonged life and improved its quality. However, these therapies have failed to significantly increase the proportion of patients who are cured. To decrease the mortality associated with these neoplasms, it is necessary to adopt public health measures aimed at prevention and early diagnosis.

Keywords: head and neck cancer; cancer of the aerodigestive tract; oropharyngeal cancer; tobacco; alcohol; human papillomavirus

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Resumen

El cáncer de orofaringe recientemente ha incrementado su incidencia, por lo que ha atraído la atención pública. Como en otras neoplasias malignas de las vías aerodigestivas superiores se atribuye a los efectos carcinogénicos del tabaco y alcohol, sin embargo evidencia reciente señala un incremento substancial atribuible a los efectos del virus del papiloma humano. Mucho se ha avanzado en relación a los conocimientos de los mecanismos moleculares y genéticos implicados en la génesis y progresión de estas neoplasias, lo que ha conducido al desarrollo de nuevas y prometedoras terapias, mas específicas y menos tóxicas, que han prolongado la vida y mejorado su calidad, pero no han logrado incrementar significativamente la proporción de pacientes curados. Si se desea abatir la mortalidad por estas neoplasias es necesario emprender medidas de salud pública dirigidas a su prevención y diagnóstico temprano.

Palabras clave: cáncer de cabeza y cuello; cáncer de vías aerodigestivas; cáncer de orofaringe; tabaco; alcohol; virus del papiloma humano

Oropharyngeal cancer is caused by tobacco and alcohol, but its increasing incidence is attributed to infection by human papillomavirus (HPV). It is usually diagnosed at advanced stage, with dismal prognosis and significant loads to health systems.

Epidemiology

In Mexico, less than 500 oropharyngeal cancer cases occur among 148 000 malignancies diagnosed each year (annual age-adjusted incidence rate of 0.5 cases per

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100 000 population and a mortality rate of 0.3/100 000).¹ The ratio between men and women is 3-5:1, and the maximum frequency occurs between 50 and 70 years-old.^{2,3} According to the Union for International Cancer Control (UICC), five-year survival rate by stages is as follows: stage I: 56.8-61.7%; stage II, 44.7-48.8%; stage III, 34.1-38.9%; and stage IV, 25.4-28.2% (CI: 95%).⁴

In Mexico, oropharyngeal cancer represents less than 10% of squamous cell carcinomas of the upper aerodigestive tract (SCC-UADT), whereby oral and laryngeal cancers make up 89% of these cases. However, in the US, Canada, Australia and Japan, an increase in its incidence has been observed, particularly among young women⁵ who do not smoke or drink but have more sexual partners and higher frequency of oral sex.⁶

Risk factors

Up to 90% of cases are caused by tobacco and alcohol use, and the magnitude of the risk is proportional to the intensity of exposure; furthermore, simultaneous exposure has a synergistic effect, which has a relative risk (RR) higher than 40.⁷⁻⁹ Based on the authors' experience, 89% of men smoke, but only 22% of women do so; therefore, other factors must be involved. The evidence suggests a causal role of HPV 16,^{10,11} but its contribution in our country has not been documented. We undertook a case-control study to document the incidence of HPV 16, 18 and 56 in the oral cavity and found a frequency of 5% in 80 cases and 2.5% in 320 controls. This study was limited to the mouth given the relative rarity of oropharyngeal cancer, and similar observations of more cases of oral cavity cancers at early ages and in non-smoking women (78% were non-smoking) that makes us suspect the causal role of HPV in oral cavity cancer. However, current figures do not support our presumption.¹² Nevertheless, we maintain that the incidence will increase because of the increasing frequency of smoking among young people¹³ and possible changes in the sexual behavior of the population. Although the HPV vaccine prevents cervical cancer precursor lesions, the efficacy of preventing SCC of the UADT is unknown.¹⁴

Screening

Even countries with a high prevalence and mortality do not rely on screening programs; however, it is good clinical practice to explore the oral cavity, oropharynx and neck in each physical examination, particularly among smokers, because early diagnosis reduces mortality.^{15,16}

Molecular pathogenesis

Unlimited cell replication is acquired by the inactivation of p16, P53 mutations and increased telomerase activity, which prevents stress-induced senescence and apoptosis in response to DNA damage.^{17,18} P16 prevents the binding of activating cyclins that drive the cell cycle. Mitogen stimulation results in the phosphorylation and inactivation of pRb, which permits DNA synthesis.¹⁹ RB1 mutations are rare, but they imply proliferative advantages.²⁰⁻²²

In contrast, 50% of ECs have P53 mutations that normally arrest the cell cycle after damage occurs to the DNA and trigger apoptosis after irreparable damage. The mutations that inactivate p53 are associated with genomic instability, tumor progression and deteriorated prognosis.²³ P53 is also inactivated by the E6 protein of HPV 16 and HVP 18.^{24,25}

EGFR overexpression occurs in 80-90% of cases and correlates with increased tumor volume, decreased sensitivity to radiation and relapse. Constitutive activation causes autocrine stimulation through the co-expression of EGFR and TGFa.^{26,27} EGFR activates signaling pathways that contribute to growth, angiogenesis and metastatic potential.²⁸

Pattern of spread

EC of the oropharynx invades and destroys adjacent structures such as the jaw and skull base. Concurrently, they gain access to regional lymph nodes and lymphatics, where they form new malignant clones.^{29,30} Distant metastases are rare (15-20%),³¹ but most affected organs are the lungs, liver and bone.³²

Field carcinogenesis

Tobacco and alcohol, the most common causes of oropharyngeal cancer, may affect extensive areas of mucous membranes. These areas often persist after surgery and can lead to the emergence of second primaries or local relapse.³³

Second primaries in patients occur at a rate of 3 to 7% per year.³⁴ In our experience, second primaries appear most often in the skin (43%), followed by the oral cavity and lungs (22% each). Tumors associated with HPV infection appear to be associated with a low risk of second primaries.³⁵ The risk of developing multiple primaries is most likely not modified by cutting out the consumption of tobacco and alcohol.³⁶

Clinical manifestations, diagnosis and evaluation

Early oropharyngeal tumors are often asymptomatic, but advanced tumors produce local pain, ear ache, cervical lymphadenopathy, trismus, odynophagia, dysphagia, hemorrhage, decreased mobility of the tongue and fistula formation. Cervical lymphadenopathy is common.

Diagnosis should be established early because of the accessibility of examination. The diagnosis is made by a histopathological study. The studies should also assess nutritional status and concurrent diseases, both of which are common in the affected population.^{37,38}

Prognostic factors

Increased risk of relapse and poorer survival are associated with the presence of lymph node metastases, increase of number and size, extracapsular invasion and localization in distant levels.³⁹ Capsular rupture doubles the risk of local and distant relapse and triples the risk of regional recurrence. In addition, the survival rate prognosis deteriorates to 50% compared to positive nodes without capsular rupture.⁴⁰ Other factors include tumor size growth rate, poor differentiation, perineural spread, vascular and lymphatic embolism, infiltrating tumor and involved surgical margins.⁴¹

Treatment

In absence of metastasis, the objective is to cure. In unresectable and metastatic tumors, which are the most common, the aim is to prolong survival maintaining quality of life.

Early tumors

Local control with radiotherapy or surgery exceeds 80%.⁴² Surgery is excellent when there is low local invasiveness,⁴³ but radiation therapy is preferred in patients with HPV infection because it results in better response and less functional impact.

Moderately advanced or resectable tumors

These tumors are treated with surgery and adjuvant treatment, but initial chemotherapy and radiotherapy is a good option if the tumor is caused by HPV⁴⁴ because it produces similar oncological results than conservation surgery⁴⁵ and possibly a better quality of life.⁴⁶ If

partial response occurs, rescue surgery is added.⁴⁷ Intensity modulated radiation therapy (IMRT) is associated with less immediate and late toxicity.^{48,49} However, its availability is limited in our country. Surgical resection requires special approaches^{50,51} and causes considerable effects that limit the social and work performance of the patients.

Treatment of regional lymph nodes

Patients without lymph node metastases still require dissection or elective neck radiotherapy, which does not improve survival, but it can improve disease-free survival, prevent reoperations, facilitate monitoring and guide the use of adjuvant therapy. Both radiation and elective neck achieve control in more than 90% of cases.^{52,53}

N1 and N2 diseases are usually treated with surgery or combinations of chemotherapy and radiotherapy. N3 adenopathies are unresectable and are treated with palliative concurrent chemoradiotherapy.

Surgical reconstruction of defects

Reconstruction is performed with grafts, pedicled flaps or surgical microanastomosed.⁵⁴⁻⁵⁷ With experienced teams, microanastomosed flaps are highly safe, but the elderly and smokers often have medical and surgical complications.⁵⁸

Adjuvant treatment

Even with complete resection, 10% of patients relapse with distant metastasis, 15-20% of patients relapse with secondary primaries, and up to 60% of patients develop locoregional recurrence. Postoperative chemotherapy with cisplatin and concurrent radiation therapy is recommended for patients with a high risk of relapse because of positive margins, extracapsular extension, perineural spread, vascular and lymphatic embolism or positive lymph nodes in levels V and IV. This treatment is associated with a 13% reduction in the absolute risk of relapse but is also associated with severe mucositis.⁵⁹ Toxicity is higher than that observed exclusively with radiation.^{60,61}

Before treatment, dental care is important because treatment causes xerostomy and mucosal damage, which deteriorates dental health. Treatment requires significant support from families. These patients often require nutritional support, which reduces treatment interruptions and improves prognosis.^{62,63}

Very advanced or unresectable tumors

Unresectable carcinomas invade the pterygoid muscles, pterygoid plates, lateral wall of the nasopharynx, hypopharynx, skull base or carotid sheath. These patients can achieve prolonged palliation with platinum-based chemotherapy and concurrent radiotherapy,⁶⁴ but other agents have been used.^{65,66}

If the adenopathies become resectable, a complementary neck dissection is performed.⁶⁷ However, patients with complete response through CT-PET and biopsy guided by US can be observed.⁶⁸ These strategies are toxic, and survival advantages disappear in adults over 70 years old.⁶⁹ Induction chemotherapy prior to chemotherapy and concurrent radiotherapy has not been associated with superior results.⁷⁰

In total, 90% of the SCC-UADT overexpress EGFR. A controlled study of cetuximab, an anti-EGFR antibody, in combination with radiation therapy for first-line treatment of advanced and unresectable carcinomas, demonstrated better DFS and overall survival (OS) in the experimental arm without increasing toxicity.⁷¹ Cetuximab increases the 5-year progression-free survival and OS rate from 36.4 to 45.6%.⁷² Therefore, cetuximab-radiotherapy might be an option among patients over 70 or those unfit for chemotherapy and radiotherapy.⁷³

Recurrent disease

Frequent relapse is related to poor prognosis, but some patients may benefit from surgery.⁷⁴ Patients with distant metastasis or unresectable relapses require palliative treatment. Cetuximab has been tested in patients who failed platinum-based chemotherapy. It improves response and progression-free survival.⁷⁵ It has also been used with first-line platinum chemotherapy in patients with recurrent and metastatic carcinomas. OS is higher compared to chemotherapy alone.⁷⁶ Six cycles of cetuximab followed by weekly cetuximab prolongs survival compared to chemotherapy alone, with a favorable toxicity profile.⁷⁷

Monitoring and prognosis

Largest proportion of relapses (80%) occurs in the first two years. Each visit includes a complete examination, and imaging studies are recommended in case of suspected relapse.

Conclusions

The unincidence of oropharyngeal cancer will increase, and it is unlikely that it will occur in early stages. Sig-

nificant efforts to reduce the mortality rate are required, such as controlling smoking and HPV infection, because mortality has not been reduced in spite of therapeutic advances.

Declaration of conflict of interests. The author declares not to have conflict of interests.

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